REMARKS

Claims 1-14 are pending. Claims 1-14 are rejected. Claims 1, 2, 4 and 12 have been amended to correct for typographical errors.

The specification on page 1, lines 8-10 has been amended to change the relationship between the instant application and a previously filed application. The instant application is now a divisional of US Application No. 09/847,113 (now US Patent No. 6,753,143, issued June 22, 2004). An amendment to the specification and an amended application data sheet are being submitted according to MPEP 201.11(V), 37 CFR 1.78(a)(2)(i) and 37 CFR 1.78(a)(2)(iii). Entry of the amendment to the benefit claim is respectfully requested.

Reconsideration of claim rejections in light of the following remarks is respectfully requested.

Claim Rejections under 35 USC 112

The Examiner has rejected claim 4 under 35 USC 112, second paragraph, for allegedly being indefinite. The Examiner states that claim 4 recites vague and indefinite language in the phrase "n protein." Applicants have amended claim 4 to recite "a protein." Applicants respectfully request withdrawal of the rejection.

Claim Rejections under 35 USC 102

Anticipation by US Patent 6,097,497 to Bauer

The Examiner has rejected claims 1-14 under 35 USC 102(e) as allegedly being anticipated by US Patent 6,096,497 to Bauer.

The Examiner states that columns 5 to 6 in *Bauer* disclose the MFS monolayer and AG electroconduit of claim 1. Applicants disagree.

Claim 1 recites modifying a metallic surface comprising contacting the metallic surface with an asymmetric monolayer forming species. According to the instant specification, an asymmetric monolayer forming species (AMFS) includes two components, at least one of which is a standard monolayer forming species such as an alkyl chain, and the other is a shorter species, for example a shorter alkyl chain or a short branched chain. Specification, p. 6, lines 26-32.

Bauer does not disclose an asymmetric monolayer forming species. As provided in section 2131.02 of the MPEP

> When a compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are **sufficiently limited or well delineated**. *Ex parte A*, 17 USPQ2d 1716, (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "**at once envisage**" the specific compound within the generic chemical formula, the compound is anticipated. **One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged."** One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676 (CCPA 1962).

(emphasis added). *Bauer* at column 6, lines 8-9 discloses that R groups of the described disulfides "can be aryl, alkyl, a combination of the two, long- or short-chain." Neither this passage nor the rest of *Bauer* discloses or explicitly names an AMFS. *Bauer* states that "[t]he nature of R and R' can be varied to balance insulation and electrical connectivity between the enzymes and the conductive layer" but this passage states or suggests nothing about the length of the monolayer forming species relative to the electroconduit forming species. The cited portion of *Bauer* does not enable one of ordinary skill in the art to draw the structural formula of each of the compounds included in the generic formula. Based on what little *Bauer* teaches relating to monolayer layer forming species in which one attachment linker is bonded to another, one of skill in the art would not "at once envisage" the asymmetric monolayer forming species of claim 1. It is further noted that a genus, assuming *arguendo* that a relevant genus were disclosed in *Bauer*, does not anticipate a claim to a species unless that species is clearly named. *See* MPEP 2131.02.

Applicants note that column 6 is the only portion of *Bauer* that discusses disulfide SAMs or any SAM in which an attachment linker is bonded to another attachment linker. The preferred or taught methods of making an SAM in *Bauer* involve using thiols that are not bonded to another attachment linker, and so such teachings are not relevant to determining anticipation of claim 1. For example, *Bauer* at column 6, lines 63-64, and in Examples 1 and 2 teaches that an exemplary R" group may be the alkyl moiety $(CH_2)_6$, but this R" group is in reference to the thiol HS-R"-OH and not to a disulfide or other AMFS. Similarly, *Bauer* in the same passages teaches forming a monolayer using 11-mercaptoundecanoic acid, but again, such monolayer is formed using a thiol, not a disulfide or other AMFS. Without teaching the AMFS of claim 1, *Bauer* does not disclose a method of contacting the claimed AMFS with a metallic surface. Applicants therefore request withdrawal of the rejection of claim 1 and claims 2-14 dependent therefrom.

The Examiner states that *Bauer* discloses that the attachment linker moiety is sulfur according to claim 5, the metallic surface is gold according to claim 6 and the MFS is an insulator according to claim 7. However, claims 5-7 depend from claim 1, and since *Bauer* does not disclose the AMFS of claim 1, it does not anticipate claims 5-7.

The Examiner states that *Bauer* in columns 5-6 discloses the insulator in claim 8 comprising "an alkyl group from about 7 to 20 carbons." Applicants disagree. Nowhere does *Bauer* disclose any **specific** alkyl moiety that forms part of an SAM having the formula MFS-A-A-AG. Mere reference to "alkyl" in column 6, line 8 is insufficient to anticipate claim 8 because as stated by the rule quoted above, when the compound is not **specifically** named, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. "Alkyl" does not sufficiently limit or delineate the possible substituents; in fact, there is no limit to the length of the alkyl group. One of ordinary skill would also not immediately envisage an alkyl group from about 7 to 20 carbons upon reading *Bauer*'s disclosure of an "alkyl" group. Any reference to an alkyl group having about 7 to 20 carbons is in the context of thiols, not a species having the formula MFS-A-A-AG. For these further reasons, claim 8 and claims 9 and 10 dependent therefrom are not anticipated by *Bauer*.

In rejecting claim 14, the Examiner states that the pendant groups of *Bauer*, which are used to covalently immobilize an enzyme, are the attachment linker of claim 14. Applicants disagree with this characterization. In claim 14 the electroconduit forming species AG is branched and attached directly to an attachment linker moiety A. The attachment linker according to claim 14 is further directly attached to another identical attachment linker moiety A according to claim 1, from which claim 14 depends. It is not clear how A can be attached to both another identical A and either an AG or MFS when A is a carboxylic acid moiety according to *Bauer*. In the event that the reference to "claim 14" in the first sentence of paragraph 3 on page 4 of the outstanding office action is in error and should read "claim 4," a response to the rejection follows.

According to the Examiner, *Bauer* anticipates claim 2 by teaching a biological species according to the formula A-MFS-capture binding ligand, wherein A is COOH, MFS is alkyl and the capture binding ligand is a protein. Nowhere is such a structure disclosed in *Bauer*. *Bauer* teaches that pendant functional groups on SAMs are "reactive with amino ($-NH_2$) or other reactive groups on proteins, or that can be adapted to be reactive with said groups, or that provide stability to enzymes by serving as either a source of hydrophilic or hydrophobic stabilization." *Bauer*, col. 6, lines 10-15. The pendant groups therefore react with the protein and "serve[] to bind enzymes to the conductive layer through the SAM." *Id.* at lines 46-47. The structure

proposed by the Examiner is not consistent with the teachings of *Bauer*. In the Examiner's structure, the protein reacts not with the carboxylic acid moiety "pendant group", but rather with the MFS alkyl group. Further, the carboxylic acid group in the Examiner's proposed structure cannot serve as a source of hydrophilic or hydrophobic stabilization because it does not come into noncovalent contact with the protein, especially if it is to serve as an attachment group to a metallic surface. In *Bauer*, an attachment group cannot simultaneously be a pendant group. The structure proposed by the Examiner is not taught by *Bauer*, and even if it were, would be insufficient to anticipate claims 2 or 4, which are not composition of matter claims.

Applicants note that the claims are drawn to **methods** of modifying a metallic surface comprising contacting the surface with an AMFS according to claim 1 and further comprising contacting the metallic surface with a biological species according to the formula of claim 2. *Bauer* does not teach contacting the metallic surface with a biological species according to the formula of claim 2 given the manner in which biosensors are constructed therein. In *Bauer*, a base layer is laid on a support and a first SAM is formed thereon. *Bauer*, col. 9, lines 38-55. A gold or silver layer is formed on top of the first SAM. *Id.* A second SAM is formed on top of the metallic layer and *then* an enzyme is attached to the second SAM. *See id.* Thus, *Bauer* teaches that enzymes are to be attached to an SAM *after* the SAM has already formed on a metallic layer. In other words, *Bauer* does not teach contacting a metallic surface with a biological species having the formula A-MFS-capture binding ligand. Claim 2, on the other hand, recites a capture binding ligand that forms a single species with the SAM *before* attachment to the metallic surface. According to claim 2, attachment of the biological species to the metallic surface can occur before or after contacting the metallic surface with the AMFS according to claim 1. *Bauer* does not teach the steps of contacting a metallic surface with the compounds of both claims 1 and 2 in any order. Therefore, *Bauer* does not anticipate claim 2 or claims 3 and 4 dependent therefrom.

Claims 11-14 are not anticipated because they depend from claim 1 and hence read on an asymmetric monolayer forming species, which as argued above is not taught by *Bauer*.

The Examiner states that *Bauer* in the paragraph bridging columns 1 and 2 discloses the method according to claim 3 wherein the capture binding ligand of claim 2 is a nucleic acid. Applicants disagree. The cited passage states very generally that DNA may be used as a binding agent in a DNA biosensor. Nowhere in the passage or in the rest of *Bauer* is specifically disclosed the species A-MFS-capture binding ligand, wherein a nucleic acid is the capture binding ligand. A mere allusion to the fact that DNA is sometimes used to detect the presence of DNA or RNA does not constitute such a disclosure. In order to anticipate, "[t]he identical invention [of a

reference] must be shown in as complete detail as is contained in the ... claim." MPEP 2131 (citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226 (Fed. Cir. 1989)). The cited passage in *Bauer* does not specifically disclose or provide any details of the compound recited in claim 3 and all the more so does not teach the step of contacting such compound with a metallic surface.

Applicants therefore respectfully request withdrawal of the rejection of claims 1-14 over *Bauer*.

Anticipation by US Patent 6,203,758 to Marks et al.

The Examiner has rejected claims 1-14 under 35 USC 102(e) as allegedly being anticipated by US Patent 6,203,758 to Marks et al.

The Examiner states that *Marks* in column 11, lines 10-16 teaches thiolipids that fall within the scope of instant claim 1. Applicants disagree.

Marks in the cited passage teaches a "disulfide of a generic structure . . . R-SS-R, where R can be an aromatic moiety, an alkyl moiety or any combination of these moieties[.]" The fact that only the symbol R was used suggests that both moieties are the same. *Marks* thus teaches a symmetric thiolipid whereas the instant claims recite asymmetric monolayer forming species.

Figure 8, cited by the Examiner, does not disclose asymmetric monolayer forming species. The first and fourth species from the left are thiols that do not fall within the scope of claim 1. The second and fifth species are cyclic disulfides that also do not fall within the scope of claim 1. According to claim 1, a monolayer forming species MFS is attached to an attachment linker moiety A but is not attached directly to an electroconduit forming species AG. Similarly, AG is attached to an A but not attached directly to an MFS. The second and fifth species of Figure 8 of *Marks*, however, are cyclic disulfides substituted with one heteroalkyl chain. These species do not contain both an MFS and an AG. Even if they did have both components, the only possible interpretation of the structure would be that the MFS and AG are directly bonded to each other, which is incompatible with the structure depicted in claim 1. The third and sixth species of Figure 8 are symmetric disulfides. For those compounds, any choice of the variables R_1, R_2, R_3, X, Y, Z, n_1 and n_2 does not change their symmetry since each of those groups is arranged symmetrically about the disulfide group. None of the species of Figure 8 therefore is an asymmetric monolayer forming species according to claim 1.

The Examiner states that *Marks* discloses that the attachment linker moiety is sulfur according to claim 5, the metallic surface is gold according to claim 6 and the MFS is an insulator

according to claim 7. Claims 5-7 depend from claim 1, and since *Marks* does not disclose the AMFS of claim 1, it does not anticipate claims 5-7.

The Examiner states that Figures 2 and 3 in *Marks* disclose alkyl groups that are in the range of about 7 to 20 carbons according to claim 8. However, one of skill in the art would understand the drawings in Figures 2 and 3 to be schematics, not drawings of actual chemical structures. The wavy lines represent chemical groups only abstractly, and no detail at the chemical level can be read from them. The descriptions of Figures 2 and 3 in the specification offer no insight as to the chemical composition represented by the wavy lines. Claim 8 is therefore not anticipated by Figures 2 and 3. In addition, claim 8 depends from claim 1, and since *Marks* does not disclose the AMFS of claim 1, it does not anticipate claim 8.

The Examiner cites Figure 5C in rejecting claims 2 and 3. As stated above, claim 2 is a method claim incorporating the method of claim 1 and further reciting the step of contacting the metallic surface with a biological species according to claim 2. Because *Marks* does not disclose the AMFS of claim 1, *Marks* cannot disclose the method of claim 1 and hence does not disclose the method of claim 2, regardless of what Figure 5C discloses.

The Examiner also cites Figure 5C in rejecting claims 9 and 10. Figure 5C of *Marks* shows a cyclic disulfide substituted with one heteroalkyl chain. As discussed above, a monosubstituted cyclic disulfide is not an asymmetric monolayer forming species according to the claims. *Marks* thus does not disclose an asymmetric monolayer forming species having an insulator comprising a heteroalkyl, and hence does not disclose a method comprising contacting such a species with a metallic surface according to claim 9. *Marks* therefore does not anticipate claim 9 or claim 10 dependent therefrom.

Continuing to refer to Figure 5C, the Examiner has rejected claims 11-14. As stated above, Figure 5C does not teach an asymmetric monolayer forming species according to claim 1. Since claims 11-14 all depend from claim 1, the methods recited in claims 11-14 are not anticipated.

Finally, the Examiner has rejected claim 4, stating that *Marks* in column 4, line 46 teaches that binding entities include proteins. Claim 4 recites a method comprising the step of contacting a metallic surface with a biological species of the formula A-MFS-capture binding ligand wherein the capture binding ligand is a protein.

Marks does not teach contacting a metallic surface with a biological species A-MFS-protein, given the manner in which *Marks* describes the assembly of the disclosed micro-circuit.

In Example 1, the binding entity is directly attached to the metallic surface. Regarding the nature of this attachment, *Marks* does not provide any detail similar to the level of detail provided in claim 2. The sparse teachings of *Marks* therefore do not disclose the biological species of claim 4 or the step of contacting such species to a metallic surface.

Example 2 of *Marks* teaches "a second exemplary method" in which "the spacer arm molecules which form the hydrogen-bonded monolayer are attached to the microelectrode surface **first, and then** the binding entity is attached directly to the spacer arm molecules themselves." *Marks* therefore attaches a binding entity to a spacer molecule *after* the spacer molecule has attached to a metallic surface. According to the claims, on the other hand, the protein is attached to the MFS *before* the entire biological species is attached to a metallic surface. *Marks* therefore does not teach contacting the claimed biological species to a metallic surface, and so does not anticipate claim 4.

In view of the above arguments, Applicants respectfully request withdrawal of the rejections of claims 1-14 under *Marks*.

CONCLUSION

Applicants believe the claims are in a condition for allowance. Early notification thereof is respectfully requested. The Examiner is invited to call the undersigned at 415.442.1000 to resolve any questions. Although Applicants do not believe any additional fees are required, the Commissioner is authorized to charge any additional fees that may be required or to credit any overpayment to Deposit Account No. 50-0310 (Docket No. 067456-5036-US01).

Respectfully submitted,

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Date September 10, 2007

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